THE BIOMETRICAL STUDY OF HEREDITY.*

By R. A. Fisher.

About twenty years ago students of heredity in this country were sharply divided by one of the most needless of the controversies in the history of science ; almost at the beginning of the century great and startling progress had been made by two groups of workers. On the one hand Mendel's laws of inheritance had been re-discovered and were being applied energetically, by what may be called, at this distance of time, the Mendelian school, to clear up problems in inheritance in many animals and plants. On the other hand the systematic study of the laws of quantitative inheritance, with especial reference to Man, had been commenced by a group of workers, whom we may call the Biometrical school. The success of both schools, by any ordinary scientific standards was brilliant ; but, by a strange fatality, connected no doubt with the temperament of the two chief protagonists, neither could find favour in the eyes of the other. It has fallen to my share, in the first of the two lectures I am giving in this course, to give some account of the discoveries of the biometrical school, and of the statistical methods developed by it ; it is worth while first to consider the place of statistics in the study of heredity in general, and its relation to evolutionary theories.

Statistics is primarily the study of populations, as contrasted with the study of individuals as such ; especially is it the study of variation which occurs among members of a population. This variation is determined by dividing the population into a number of different types and discovering, by an enumeration of a sufficiently large sample, the frequency with which each of the different types occurs. To take an example of the process at its simplest, children at birth vary in their sex ; two distinct types are observable, male and female ; to determine the frequency ratio of these two occurrences is a typical statistical problem, and an investigator who hopes to draw conclusions from the frequency ratio, for example that 51% of the births are of males, is using the statistical method (at its simplest), and may be contrasted in this respect with other workers who base their conclusions on the morphological and physiological differences observable between individuals of the two sexes.

Now the difference in method between Mendel and his contemporaries is that, whereas they appear to have been concerned wholly with the morphological study of individual parents and offspring, Mendel interested himself in the frequency ratio with which different types occurred, and bred sufficient numbers to determine these frequency ratios with some accuracy. Consequently he has led immediately to the famous Mendelian ratios, which are, of

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course, the ratios of the frequencies with which different types of offspring occur. Mendel was in fact the pioneer of the statistical method in the study of heredity ; and it happened that the statistical method of research was the fruitful one. It might have been otherwise ; there is a belief held by certain horse breeders for example, that the body of the offspring takes after the mother, but the mental disposition takes after the father. Generalisations of this sort would have been of great value, if they had been true. As it is, no generalisation of this character has been established, and the whole development of modern genetics has been the exploitation of the line of thought opened up by Mendel. Mendel's observation for instance, that in a certain cross with garden peas, the hybrid generation produced just three times as many tall plants as short plants, has happened to be more fruitful than any amount of investigation of the morphological nature, or the physiological causes, of the shortness or tallness.

The second great advance in Mendelism, which has enabled us to locate the physical bases of the Mendelian factors as systematically arranged units in the structure of living matter, was equally the product of the statistical method. It was found that certain factors were linked in their inheritance ; so that if a pair of such genes were received by an individual from the same parent, they would be handed on to his offspring in more cases than not as an undivided unit. Only in the minority of cases, in which, as we now say, *crossing over* had taken place, would the grandchild receive a pair of such genes through the same parent, but from different grandparents. This phenomenon requires a considerable number of offspring to detect it, and still more to make an accurate estimate of the percentage of crossovers—a purely statistical frequency ratio found by counting the numbers of the different types of offspring appearing. Consequently, the important conclusions to which the study of linkage has since led, only began to be drawn when American workers began to exploit the extraordinary advantages of the American fruit fly, *Drosophila*, as a subject for genetical study. From that time it has been possible to carry out experiments quickly, and with statistically sufficient numbers; all the linked factors fall into distinct linkage groups ; the linkage relations showed that within each group the genes were arranged in order like beads on a string, so that once their position had been located, the intensity of linkage between any two genes could be predicted ; and the linkage groups themselves, or strings of genes, were identified with certain dark staining bodies, called chromosomes, which can be observed in the nuclei both of the germ cells and of other cells throughout the body.

With these successes of the statistical method in mind, let us turn to the work of the biometrical school, remembering that their work had borne much of its fruit before the re-discovery of Mendel's laws, and that even after that event, to judge by the writings of their leaders, the applicability of Mendelian inheritance to Man was either denied or ignored. The outstanding feature of the biometrical work was the elaboration of advanced statistical methods ; methods which have since proved their value, not only in the study of inheritance, but in every branch of modern social enquiry. It is obvious that such special methods were necessary. Man presents genetical material very different from the American fruit fly. A typical Drosophila experiment, if performed with Man, would take about 200 years ; indeed, it would take at least as long as this to perform the preliminary purification of the stocks ; then again, human beings are not available for experimental breeding. Against these disadvantages Man is in certain ways a peculiarly available source of genetical knowledge ; he exists in large numbers, and in a state of domestication ; he keeps his own pedigrees, at least for near relatives, and may easily be induced to take a great interest in his own measurement. Besides, even the most specialised geneticists would admit that he is a very important animal to know something about. To exploit these advantages presented by man as an object of genetical study, was the principal task attempted by the biometers.

With these differences in material, too, goes a great difference in the characters open to study. The round or wrinkled shape of garden peas, or the red or white eye of Drosophila, presents clear-cut alternatives with, at most, a trifling minority of doubtful intermediates. In Man, except for a few rare abnormalities such as Albinism, such clear-cut alternatives do not present themselves. If we concentrate upon any such character as Stature, or Intelligence, all intermediate types are found, within more or less wide limits of variation. The frequency distribution actually found, as Quetelet, the Belgian astronomer, pointed out in the middle of last century, is of the important form known as the normal curve of frequency of errors, or simply as the normal curve. This curve, which owing to its theoretical importance is very well known, appears to represent with considerable accuracy, the distribution of a large number of different measurements, bodily and mental, in human populations.

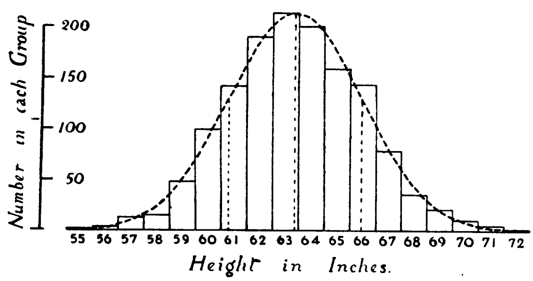


FIG 1.

The general features of the normal curve are very simple. The histogram shows the actual numbers observed in different intervals of stature ; the interval is one inch ; the sample illustrated is of about 1,500 young women, largely students, or sisters of students, at University College. The curve represents what we should expect if a very much larger sample of the same population could have been obtained and illustrated on the same scale. It is obvious that the largest classes are those of about medium height. Very tall and very short individuals are much more rare ; near the extremes the frequency falls off with great rapidity. If a thousand times as many cases had been available, the total range would have been somewhat extended, but the number of new classes needed would have been surprisingly few, if the distribution were accurately normal.

The fact that actual measurements conform, at least approximately, to a mathematical law, introduces a great simplification into the whole question of variation. For nearly a century investigators, such as economists and meteorologists, who are confronted with marked variation, have been in the habit of calculating some sort of average value, and thereafter ignoring the fact of variation. Clearly this procedure is very inadequate, but it was not obvious what else could be done. However, if the distribution is normal, we have only to take one step further to give a complete account of the variation ; we calculate the mean, and in addition calculate what is known as the standard deviation. Geometrically the standard deviation is the distance from the centre of the curve to the steepest point on the slope ; arithmetically it is found by taking the difference between each observation and the mean of all ; then the average of the squares of these differences is called the *variance* of the curve, and the square root of the variance is the standard deviation. In any case, it is clear that the standard deviation measures how spread out the population is on either side of the mean. With this group of measurements (Fig. 1) the variance is about 6.65 square inches, and the standard deviation is 2.58 inches.

There is one technical term which I have just used, which requires a further explanation. The amount of variation may be measured either by the Standard Deviation, or by its square, the Variance. When we come to consider the causes of variation, the latter provides the more useful measure. For this reason, that when two independent causes are at work causing variation, the total variance produced is simply the sum of variances produced by the two causes acting separately. For example, one of the causes of differences in stature is difference of ancestry, the remainder of the causes of variation in stature are those causes which produce variation in stature among girls with the same ancestry, in fact which cause differences in stature between sisters. From measurements of pairs of sisters it is possible to divide up the total variance into two parts. One part representing the differences due to ancestry, the other part representing the other group of causes. If, then, we use the variance as the measure of variability, we can use it to analyse out the fractions of the variability due to different causes ; whereas using the standard deviation no such analysis is possible.

Before leaving the question of the normal distribution of human measurements, it should be mentioned that there is evidence that in some cases the normal law is not exactly, but only approximately realised. In measurements of Cubit, the length of the forearm, Pearson noticed a small group of specially large measurements, or giants, in his records ; such an exception is of importance for it is exactly what might be looked for in the supposition, which we will consider more fully later, that variations in human measurements are due to a larger number of Mendelian factors.

The direct attempt, not only to demonstrate the existence of heredity, but to measure its intensity, in mankind was initiated by Galton. The method, and the general results of investigators based upon that method, are best exhibited by a table showing the distribution of a large number of pairs of relatives, for example, Fathers and Daughters, both in respect of stature.

HEIGHT OF FATHER (INCHES)

HEIGHT OF DAUGHTER (INCHES)	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	TOTAL
53					1													1
54																		–
55							1											1
56					1		1		1									3
57	1		1	5	1	2	1	2										13
58		1		2	1	1	2	5	3									15
59	2	2		6	4	5	7	11	3	4	2	1	1					48
60	2		2	8	6	13	18	20	12	8	5	3	1	1				99
61		2	2	9	12	13	24	23	20	17	10	4	3	2				141
62	1	2	2	5	11	22	26	34	28	24	15	14	5		1			190
63			2	5	9	11	27	37	37	32	26	16	8	3				213
64			3	3	3	9	24	18	28	32	35	24	12	6	1	1	1	200
65				1		11	12	9	20	31	26	22	15	4	4	2	1	158
66			1		2	3	8	9	16	26	27	21	18	7	4		1	143
67						1	5	7	4	14	13	11	12	5	4	2		78
68								1	3	5	5	6	5	4	2	2	2	35
69					1		1		1	1	3	7	2	2	2	1		21
70										1	1	4	1	2	1			10
71										1			1	1	1	1		5
72										1								1
TOTAL	6	7	13	44	52	91	157	176	176	197	168	133	84	37	20	9	5	1375

FIG. 2.

Such a table is called a correlation table. Each case, consisting of the values of the stature of a father and of his daughter, is placed in the column corresponding to the height of the father, and in the row corresponding to the height of the daughter. The table is a very compact summary of a very large number of facts, and a great deal may be learnt merely from the inspection of it. The division of the table into columns sorts out the population according to the height of the father ; each column shows the distribution in stature of daughters of fathers of a given height. There is considerable variability within each column, though not quite so great as the general variability, shown in the margin, of the heights of the whole population of daughters. The columns are all about equally variable, each with variance about $\frac{3}{4}$ of that of the general population ; but they clearly have very different mean values. The average height of the daughters of tall fathers is much greater than that of the daughters of short fathers. Very tall daughters of very short fathers, and *vice-versa* do not occur ; the table is empty in these two quarters. Evidently these two measurements are quite closely associated ; the extent to which they are associated may be calculated from the observations, by means of a quantity known as the *Correlation Coefficient.*

The correlation coefficient is a numerical measure of association, which is now widely used, especially in its economic and sociological applications. For the present we may regard it merely as a number, positive or negative, lying somewhere in the range -1 to $+1$. When two variates are independent the correlation between them is zero. The closer the association the higher is the correlation. The correlation coefficient between relatives may therefore be regarded, not only as a measure of the strength of inheritance, but as a measure of nearness of relationship. At first sight we should all suppose that our fathers and mothers stand to us in a closer relationship than do our brothers and sisters, but it is found that the correlation between brothers or sisters, or between brother and sister is in fact slightly higher than that between parent and child.

For stature, the parental correlation is about ·51, the fraternal correlation about ·54 ; and these small differences have always been found in good and sufficiently extensive data. We must remember that we are related to brothers and sisters through both parents, and this explains why the fraternal correlation should not be much lower than the parental correlation. With half brothers, who are only related through one parent, we should probably have a correlation of about ·25, corresponding to a parental correlation of about ·50. This consideration does not explain why the fraternal correlations should be larger than the parental, and this is another fact to which I hope to return in a later section.

In most cases we have no doubt which relationships are nearer and which are more distant ; for example, we are ordinarily related to a cousin through only one uncle or aunt, and we may be sure that the relationship of cousinship is more distant than that of uncle and nephew. There is one interesting case where the correlations may help to clear up a difficulty. How closely related are twins? Two modes of origin have been commonly accepted for twins. In one mode the two twins are ordinary brothers or sisters who happen to have been conceived and born at the same time. For such cases the correlation should be slightly above ·5. In the second mode, it is supposed that the individual at a very early stage, splits into two equal parts ; in such a case the genetic constitution of the two parts should be identical, and if the genetical factors are of importance very high correlations may be expected—something like ·9, or over. Actual data for twins is extremely scanty, but such as exists suggests that twins form a homogeneous group, with an intermediate correlation of about ·75 to ·80. This is a fact, which if substantiated by further data, must require an entirely different view of the origin of twins.

Before considering the manner in which the correlation coefficient measures the intensity of inheritance, it is convenient to define another quantity (or rather two other quantities) which may be calculated from the correlation table.

It is obvious from the table (Fig 2) that when we increase the height of the fathers by 1 inch the average height of the daughters is increased. This increase is quite regular from one side of the table to the other. Within the limits of sampling errors, for every inch by which we increase the height of the fathers, the average height of the daughters is increased by very nearly half an inch. This is shown more clearly in the following figure, prepared from the same data.

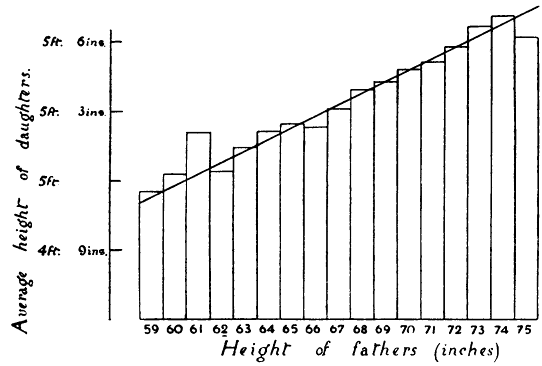


FIG. 3.

The amount by which the average height of the daughters increases for unit increase in the height of the father is evidently a most important biometrical constant. It is called the *regression coefficient* of daughter's height upon father's height. The numerical effect of *selecting* the parents of the next generation may be directly measured by means of the regression.

Now, if we go back to the correlation table, we may equally calculate another regression coefficient. The rows show the heights of the fathers of daughters of a given height. If we increase the height of the daughters by one inch, by passing from one row to the next, it appears that the average height of the fathers is increased, quite regularly all the way from the top of the table to the bottom. Fig. 4 shows the average height of the fathers of

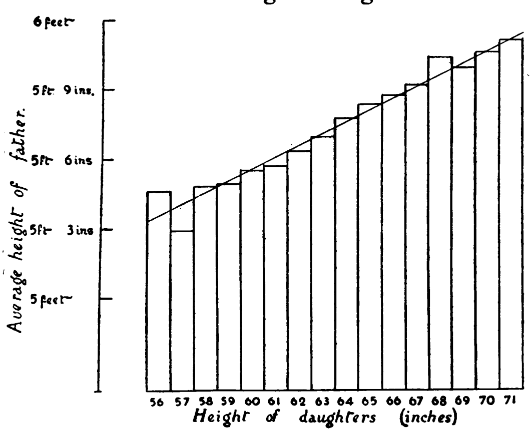


FIG. 4.

daughters of a given height. And again for each inch in the daughter's height, the average height of the fathers is increased by very nearly half an inch.

These two regression coefficients, both very nearly equal to one half, throw a great deal of light on the interpretation of such statistics. To begin with, these statistics do not prove that daughters inherit their height from their father ; if they proved that they would equally prove that fathers inherited their height from their daughters, which is absurd. What they prove is that the heights of fathers and daughters are influenced by the same causes and it is generally agreed on quite other grounds, that the important cause of this similarity, is that daughters have a great deal in common with their fathers in their hereditary constitution. We know in fact that the daughter originates partly from a minute fraction of the father separated for the purpose of building up a new organism, and this fact warrants us in speaking of the resemblance of fathers and daughters as a hereditary resemblance.

In the next place the regression shows us immediately what will be the effect of selection, in modifying the population. Darwin put forward the theory that species were being gradually modified, because the parents of each generation were not a random sample of the offspring of the last generation, but were a specially characterised group selected by the conditions of survival and of reproduction. The regression coefficient shows just how effective such selection is ; supposing for a moment that the selection was confined to one sex only. If, in every generation the men selected to be fathers exceeded the average height by only two inches, the general average of the population would increase by one inch in every generation ; by three inches in a century, or by a foot in 400 years. In quite short historical periods such a selection is capable of modifying the physical characters of a race, to an extent greatly exceeding the differences ordinarily observed between different races. Historians and sociologists have taken too little account of these facts ; they are inclined to assume that races of men are constant quantities. It is indeed probable that the physical characters, such as stature, have not been subjected to any very severe selection during civilised periods ; but there is no reason to doubt that a similar selection may have been acting on the mental type, and there is indeed much evidence that such selection has been, and is at this time, in progress.

The simplest definition of the correlation coefficient is that it is the geometric mean of the two regressions. If, as in this case, the two regressions are nearly equal, the correlation coefficient has the same value, approximately one half, or perhaps more nearly ·51. We are now in a position to consider what is meant by saying that the correlation coefficient is a measure of the strength of inheritance. First we may notice that the correlations with the mother are of equal size, with the correlations with the father, neither greater nor less ; also the correlation of parents with their sons are neither greater nor less than those with their daughters ; all four values are in close agreement, and we may speak of them all as the parental correlation coefficient. In some measurements the parental correlation is somewhat lower than it is in stature, but never very much lower ; we may take the parental correlations for physical measurements to be usually about ·46, and the fraternal correlation about ·50 ; for stature the best values are about .51 and .54. Now any factor, or experience, which affects stature independently in parent and child, as, for example, the age of onset of infectious diseases might be supposed to do, will tend to lower the correlations. In general, any environmental influence will tend to lower the correlations between relatives; so that if we had two populations similar in respect to inheritance, one living under a very uniform environment and the other under very diverse environmental conditions, we should expect the latter to show the lower correlation, if environment were at all influential upon the characters studied. Equally, if we had two populations with the same range of environmental influence, one of great genetic uniformity, and the other of great genetic diversity, we should expect the latter to show the higher correlation coefficients. In this sense it may be said that the correlation-coefficient provides a measure of the relative importance of hereditary and environmental influences upon the character studied. This was the position taken up by the early biometers. In the main it may be said to have been justified by later research, but it is open at first sight to the criticism that possibly other factors, besides the relative importance of heredity and environment, may influence the value of the correlation. One important factor of this sort is the correlation between husband and wife. In stature, for example, husband and wife are markedly correlated, tall women tending to marry tall men, and *vice versa* ; this probably explains the higher correlations found for stature than for other physical measurements, and clearly it has nothing to do with the relative importance of heredity and environment.

Assuming that, in the parental correlation, they had a measure of the strength of heredity, the early biometers sought to estimate how high the correlation would be if heredity were the sole cause of variation, that is, if environmental effects were wholly negligible. For this purpose it was necessary to find some character upon which environment was probably without effect. The character chosen was the depth of pigmentation of the eye. This character cannot be directly measured, but eyes may by examination be placed in broad classes in respect of degree of pigmentation, and from such a broad classification an estimate of the correlation, comparable with that obtained from measurements, may be made. When eye colour data were examined in this way it was found that the parental correlation for eye colour agreed surprisingly well with that obtained from the physical measurements, having a value .50 against .46. We need not enter into a detailed criticism of the methods by which this result was obtained, or of the validity of the conclusions drawn from it. At the present time the argument seems to me to be of only historical interest, but it serves to show on what grounds the biometers of about twenty years ago were led to conclude that variation in the physical measurements was due almost exclusively to the innate hereditary factors.

Having reached this point it was natural to attempt to extend the conclusion to the mental and moral qualities. For this purpose a large investigation was made of the fraternal correlation in school children ; the children were classified in such characters as vivacity, conscientiousness, ability, etc., and the correlation was estimated as before. The results were in striking agreement with the results of physical measurement ; the degree of resemblance in these mental and moral qualities is evidently very nearly the same as for the physical characters determined by growth. The coincidence of the two sets of values, and the concordance of each set within itself, strongly suggests that the cause of resemblance is the same in every case, and that the conclusion is justified that mental and moral qualities are as strongly inherited, and consequently as easily influenced by selection as the physical characters are known to be.

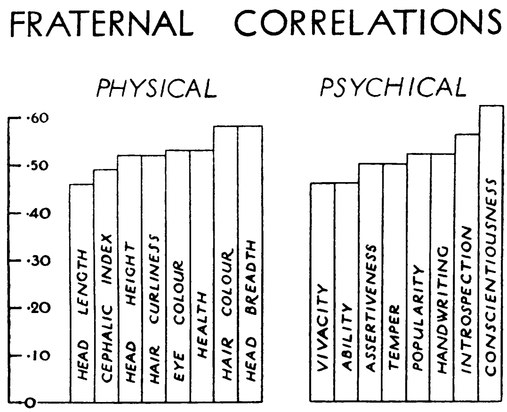


FIG. 5. FRATERNAL CORRELATIONS FOR PHYSICAL AND PSYCHICAL CHARACTERS.

Before leaving the work of the early biometrical school, I must allude to one result which has been entirely misunderstood, even in otherwise important modern works. It will be remembered that if we were to select fathers of the next generation to be on the average two inches above the average stature, their offspring will be on the average only one inch above the old level. The sons will be on the average half way in stature between their fathers, and the average of the generation from which their fathers were selected. They will apparently have lost ground compared to their fathers, and will have reverted to some extent to the old level. This phenomenon has been called " regression to the mean," a use of the term regression quite different from the technical meaning of the term explained previously. Many have thought that this " regression to the mean " entailed an undoing to the effect of selection, and have even stated that, continuing generation after generation it would entirely undo the effect of selection. Such a view shows a complete misunderstanding of the statistical facts. " Regression to the mean " in no way implies any undoing of the effect of selection. Its first and most obvious cause is that we have supposed only the fathers to be selected ; the offspring are the products of both parents, and the most that could be expected is that they should be as tall relatively to the mean, as the average of the two parents. With selected fathers and unselected mothers we should not expect to obtain much more than half of the additional height of the fathers. But this will not explain the whole of the effect ; if we selected both parents there is still some tendency for the offspring to return on the average somewhat towards mediocrity, about one fifth of the way. This effect finds its explanation in the fact that the actual stature is not quite a perfect measure of the genetic potentiality for begetting or bearing tall children. If environmental effects, for example, were of any importance in determining stature, in selecting tall parents we should be selecting, not only those of high genetic potentiality, but to some extent also those who had experienced an environment favourable to tall stature. The average of the next generation, reared in an average environment, would for this reason alone be somewhat shorter than their parents. But the effect would stop there ; the third generation would not show any further regression.

An effect, similar, in this way, to variations in environment, and of much greater numerical importance in respect to human measurements, is produced by Mendelian factors. As is well-known these factors generally show complete dominance, in such a way that the hybrid or heterozygote is not intermediate between the two pure bred types, but wholly, or almost wholly, resembles one of them. For this reason in choosing a tall parent we will often be choosing a heterozygote for some factor in which tallness is dominant, and a proportion of the offspring will show the short character. Equally for factors in which shortness is dominant, the matings of pure tall with pure short will produce all heterozygous short offspring. It may be shown that the effect of dominance in Mendelian factors will reproduce numerically the effects observed in the regression to the mean in human measurements, so that it is not necessary to ascribe more than an insignificant fraction of the total to environmental effects. The effect of dominance, like that of environment, in producing "regression to the mean," is limited to the first generation. In fact, the effect of selection is exactly measured by the regression coefficient as first explained, and there is no tendency for the effects of selection to be undone in future generations.

To summarise briefly the achievements of the biometrical school

(i) They have shown that human measurements are approximately distributed in the normal distribution, but have shown also that in large samples perceptible deviations from this simple distribution may be observed.

(ii) They have developed methods of measuring the degree of resemblance between relations, and have shown that this degree of resemblance is almost the same for (a) for the physical measurements; (b) for characters unaffected by environment, such as eye colour ; (c) for mental and moral qualities.

(iii) They have given a direct measure of the effectiveness of selection, and have shown that by the action of selection human populations may be modified greatly in relatively short historical periods ; and, indeed, far more repidly than it is necessary to suppose that species of animals and plants have in fact usually been modified, during the course of evolution. There is a wide margin to spare in the action of selection, and even slight and indirect selective effects, may have been very influential.

In what follows I propose to examine the evidence for and against the proposition that all inheritance is in reality reducible to the Mendelian system ; and that the phenomena of inheritance in Man are wholly due to the interaction of a number of Mendelian factors. With this question in view let me call to mind the four facts which have appeared in this lecture.

(a) The approximately, but not quite exactly, normal distribution of human characters.

(b) The conclusion of the biometers that a parental correlation of about ·51, and a fraternal correlation of about ·54 were compatible with an almost complete predominance of the hereditary influence.

(c) The fact that the fraternal correlation is regularly slightly in excess of the parental correlation.

(d) The existence of a slight, but definite, tendency of the offspring of selected parents to revert (about one fifth of the way) towards the mean of the general population.

Remembering that the biometers rejected or ignored the discoveries of the Mendelians, and that Mendelian workers have equally ignored the discoveries of the biometers, these facts have, as I hope to show, a very striking bearing on the nature of human inheritance, and indeed on general evolutionary theory.

With these four points in mind, we are in a position to consider the evidence for the applicability of Mendel's laws of inheritance to mankind.

The first point to notice is the widespread occurrence of Mendelism among living things generally. Mendelian inheritance has been found in mice, rats, cats, sheep, pigs and oxen, and indeed in all domestic animals which have been bred experimentally; it is not confined to mammals ; well-known examples have been found in birds, and more recently in fishes. Among invertebrate animals, some of the most important investigations have been made with insects, and perhaps equally valuable material has recently been found among crustaceans. The phenomenon is not even confined to the animal kingdom, but has been found to be equally universal in plants. On a general survey it would appear that Mendelian inheritance is probably co-extensive with sexual reproduction in the animal and vegetable kingdoms. This wide diffusion cannot fail to suggest that Mendelism plays an important and fundamental part in the inheritance of all sexual forms of life. The conclusion is strengthened by the fact that sex differences themselves in both animals and plants are inherited in the Mendelian manner. Although establishing its importance, these facts do not prove that Mendelism is the only form of inheritance, because the characters open to Mendelian research, and which are usually chosen for investigation, are only those strongly contrasted characters, which can be easily classified into definite types. But no other form of inheritance has been discovered, and until it is discovered, there is a presumption that all inheritance will be found to fall into the Mendelian scheme

The next point is that the mechanism necessary for Mendelian inheritance undoubtedly exists in Man. Many cases are well-known in which marked abnormalities in Man, follow the Mendelian rules One of the most striking examples was recently published, without any reference to Mendelism, in the Draper's Company Research Memoirs. There is a defect of the eyes known as Night Blindness, in which the patient has dfficulty in seeing in a faint light. In the more usual form the effect is progressive ; it increases in severity, and leads to total blindness. In another form the defect is described as Congenital and Stationary ; it appears early in life and does not increase in intensity. This Congenital Stationary Night Blindness is inherited in a definitely Mendelian manner. (Figs. 6 and 7).

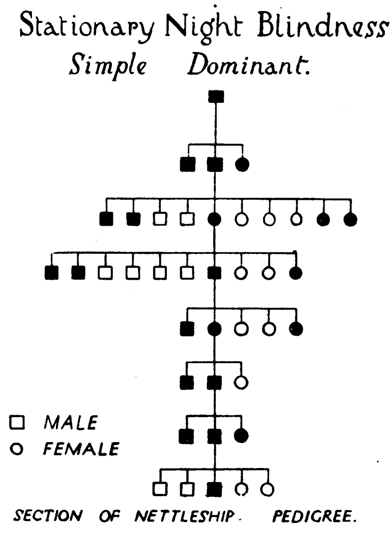


FIG. 6.

These are but two examples of Mendelian inheritance in Man. The number of rare abnormalities which behave in this manner is now known to be very great. Most of those known are dominants, probably because it is easy to trace the inheritance of a dominant ; recessive defects appear spasmodically, and no similarly afflicted relative may be known. The only recessive defects which are easy to trace in inheritance are the sex-linked recessives ; and it is noticeable that of the sex-linked abnormalities all the cases reported so far are recessive ; this suggests that if only they could be traced, recessive defects would be found to be even more numerous than dominants.

These two preliminary observations show that Mendelian inheritance is probably of importance, and perhaps the only form of inheritance in all sexual organisms, and that the mechanism needed for

Mendelism certainly exists in Man. We must now consider what evidence is available for judging whether or not the quantitative characters in Man are also inherited on the same system, and this is of special importance, not only because they are almost the only quantitative characters in the animal kingdom which have been much studied, but because they include those mental and moral qualities to which the great achievements of Man must be ascribed, and by which his future achievements must be conditioned.

The possible alternative to Mendelian inheritance is a system of blending inheritance. In Mendelism the individual genes pass from generation to generation entire and unchanged ; as an alternative, it is possible to imagine a system in which the parental contributions are permanently blent in the offspring, who will, apart from mutation, be exactly intermediate in genetic composition between the parents. Such a system is not only possible, but has in the past been widely

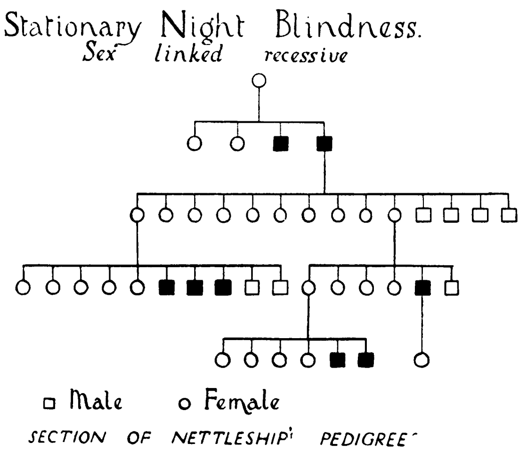


FIG. 7.

accepted. There is one contrast between this system and that provided by Mendelism, which has, I think, been entirely ignored.

If we consider the variability of a population, or in particular, the numerical quantity which I have called the variance, there must exist some mechanism by which this variance is maintained at an approximately constant value from generation to generation. In Mendelian inheritance this mechanism is provided by the segregation of factors ; the factors themselves are unchanged, and are merely shuffled and combined in new combinations in each generation ; apart from selection there is no reason why the variance should not be maintained indefinitely. On the other hand, with blending inheritance, the variability can only be maintained by the constant occurrence of new mutations. Without mutation the offspring of two parents would be all alike genetically, and intermediate between the parents ; consequently they will cluster more closely round the general average than did their parents. It may be shown, in fact, that the variance of the population would almost be halved in each generation. For the variance to be maintained in value, fresh mutations must occur in every generation to such an extent that at any time nearly one half of the total variance would be due to new mutations, about a quarter to mutations in the last generation, and only a small fraction to old mutations dating back several generations.

I think this conception of blending inheritance, with the variability maintained by constantly occurring fresh mutations, deserves careful consideration, if only because there can be no doubt that it was in this way that Charles Darwin imagined inheritance and variation to take place. Much has been written on the assumption that modern advances in genetics had rendered Darwin's views obsolete, but on examination, I think that this is the only point of importance upon which Darwin might wish to revise his early opinions. The novelty of the Mendelian system of inheritance is that it renders the continual occurrence of numerous fresh mutations unnecessary, and if Mendelism provides the only means of inheritance we must suppose that mutations are relatively very rare. On the other hand, if it can be shown that mutations are in fact very rare, it follows conclusively that blending inheritance can be of little or no importance.

Fortunately a series of experiments have been carried out with many animals and plants, which do demonstrate the extreme rarity of mutations. These experiments are known as pure-line experiments, and were instituted with very different ideas in view ; one of the earliest and most famous was that of Johanssen with beans. The bean used is ordinarily self-fertilised ; cross-fertilisation is quite rare ; the plant may be maintained apparently indefinitely by self-fertilisation. By continued self-fertilisation of the progeny of single beans, Johannsen was able to obtain what are called " pure lines," that is, families of individuals identical in their hereditary properties. Within such pure lines, the selection of the largest or the smallest beans was absolutely without effect ; each set bred progeny of the same size. The genetic composition of the pure line remained unchanged from generation to generation. Out of many thousands of individuals bred, at least one, and perhaps more than one, definite heritable mutation has occurred, but the experiments show conclusively that mutations do not occur, as Darwin supposed, in almost every individual of every generation, but sporadically and with extreme rarity. Pure-line experiments with other organisms have led to the same final result ; mutations have usually been found, but with extreme rarity, among an immense number of non-mutant individuals. This evidence appears to me to be decisive for rejecting the theory of blending inheritance in quantitative characters, and for admitting that the genetic factors underlying such characters must segregate, as do Mendelian factors.

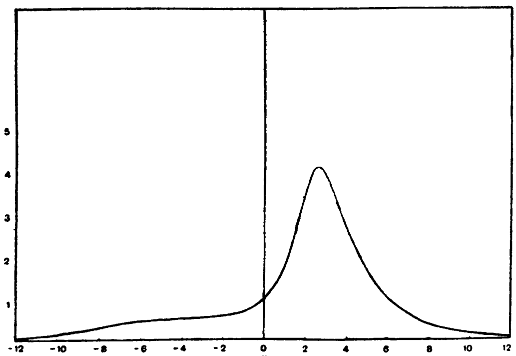
The evidence in favour of blending inheritance was drawn almost entirely from quantitative characters in man, such as stature or skin colour. Crosses between races widely different in such characters usually give intermediate offspring ; the characters appear to blend, but it by no means follows that there is any blending of the underlying genes. Such characters in man thus afford a test case of the universal applicability of Mendelian theory. There are two characteristics of Mendelian factors to be looked for, one is Segregation, the other is Dominance. The discoveries made by the biometrical method provide definite evidence of both these characteristics.

First, let me recall that the early biometers concluded that a fraternal correlation of ·54 was compatible with the assumption that the character in question was wholly, or almost wholly, determined by inheritance. This conclusion was based on a variety of considerations, some of which are perhaps open to criticism, but which as a whole must carry considerable weight. The conclusion is really a surprising one, if we consider what it implies as to the causes of variation. The fraternal correlation is the correlation between children of the same parents, and therefore between persons whose whole ancestry is identical ; a fraternal correlation of ·54 represents a condition of affairs in which 54% of the variance in the population may be ascribed to differences in ancestry, and 46% to differences among persons of the same ancestry. How can we say that inheritance is all-important if persons of the same ancestry have a variance equal to nearly half of that of the population at large? This question was never faced by the biometric school. To what causes can this 46% of the variation be due, if not to differences in environment? We cannot, in view of what is now known, ascribe it to mutations. There remains only the possibilty that it is due to the Mendelian segregation of the factors in which the parents were heterozygous. Owing to segregation persons of the same ancestry will differ in heritable factors. This supposition affords not only a qualitative, but a quantitative explanation of the facts ; segregation should produce about half of the total variance.

Further evidence, that more is heritable, than persons of the same ancestry always inherit in common, is afforded by the case of twins. The correlation between twins is, as I previously mentioned, much higher than that between ordinary brother and sister ; the value is about ·75 or ·80. This shows that twins are much more alike than persons of the same ancestry generally are, and this fact again can, I think, only be explained by segregation. Brothers are exactly alike in ancestry, but they differ considerably in their hereditary qualities.

There is thus considerable evidence of segregation in the quantitative characters in man ; the evidence in favour of the second characteristic of Mendelism, namely of dominance, is at least equally cogent. This appears when a systematic attempt is made to interpret the biometrical facts in terms of the theory that such a quantitative character as stature is determined by a large number of Mendelian factors. The suggestion that such a theory might explain the facts, was, I believe, first put forward by Yule, about 1902. Soon after, Pearson, treating a very limited and narrowly restricted case, came to the conclusion that the Mendelian theory required that the parental correlation coefficient should be as low as ·33, whereas in fact the observed values are about ·46. This conclusion seemed to indicate that Mendelism could not explain the facts. At a later date Yule suggested that if it were assumed that the Mendelian factors concerned did not show any dominance, but that, in each case, the heterozygote was just half way between the two pure types, then the parental and fraternal correlations would both be raised to ·50 ; if in addition the measurement was affected by environmental factors, both correlations would be lower.

This was the position when I first attacked the problem presented by the biometrical facts in relation to the Mendelian theory of heredity. In attempting to throw light upon the problem I was guided by two facts. Without dominance the parental and fraternal correlations are equal ; the effect of dominance is to lower them both ; but its effect on the parental correlation is twice as great as its effect upon the fraternal correlation. The fact that in every character examined the fraternal correlation is always found to be somewhat greater than the parental correlation, thus seemed to be an important indication that dominance was present ; in fact, it should be possible to estimate the extent to which dominance actually occurred among the factors concerned, from the difference observed between the two correlations. In the second place I observed that the correlation between husband and wife, which is positive in the cases for which data is available, would tend to raise both the parental and the fraternal correlations, whereas the effect of environment, like that of dominance, would tend to lower them. When we know all three values, (i) the parental correlation ; (ii) the fraternal correlation ; and (iii) the correlation of husband and wife (the marital correlation), it is possible to estimate independently the extent to which dominance is present, and the extent to which environmental influences contributed to the variance. This method was applied to three different human measurements, Stature, Cubit, or length of forearm, and Span,



$$df \propto \frac{dx}{\sqrt{e^{-x}\operatorname{sech}^2 \tfrac{1}{2}x + k^2\cosh^2 \tfrac{1}{2}x}} \quad k = \cdot 1.$$

FIG. 8. DISTRIBUTION CURVE.

or the full extent of the body width with extended arms ; data from these three measurements being available. All gave concordant results. The environmental influence in each case is probably about 2%, and not more than 5% of the whole. The effect of dominance came out to a surprisingly high value. The quantity used to measure it, called the dominance ratio, gave a value of ·32. It was some years before I could understand why the value was so high, for in making my calculations I had assumed a population breeding without selection. It was not at all obvious, at the time, that selection would influence any of the results; only later, in studying the effect of selection on the distribution of Mendelian factors, did I hit on the fact that in a population long subject to selection the dominance ratio for ordinary Mendelian factors should always have the same value, namely $\frac{1}{3}$, or ·33. That was the final confirmation needed to bring the biometrical facts into complete agreement with the Mendelian theory. The low value of the environmental effects showed that the "regression to the mean" shown by children of selected parents was due chiefly to dominance, and only very slightly to environmental effects. The same degree of dominance will explain both this effect and the difference between the fraternal and the parental correlations, and finally the degree of dominance required will be that appropriate to ordinary Mendelian factors in a population subject to selection.

The actual distribution of Mendelian factors which led to this result is of some interest in other ways.

Fig. 8 shows the theoretical distribution curve for a large number of factors, such as those affecting the physical measurements, and no doubt also the mental measurements in mankind. In the central line the dominant and the recessive genes are equally frequent in the population. On the left the dominant genes are rare and the recessive genes common ; on the right we have the factors with rare recessives and common dominants. The height of the curve shows the frequency of each type of factor.

When a dominant mutation occurs it appears at the left hand end of the curve ; if it is unfavourable to survival selection keeps pushing it to the left, keeping it rare, so that it never gets far and is finally exterminated. If it is favourable to survival, it becomes more numerous, at the expense of the corresponding recessive, it crosses the left side of the curve comparatively quickly, but as the recessive becomes rarer selection becomes less and less effective, and it may remain for long in the great accumulation of rare recessives before it is finally exterminated. Similarly, if a recessive mutation occurs and survives, it will be added to this accumulation in the region where selection is feeble. If the new gene is unfavourable to survival it will never get any further, and will no doubt ultimately be exterminated ; if it is a mutation favourable to survival, it may pass slowly through the region of feeble selection, advancing more and more rapidly across the central and left hand region, and finally exterminate the relatively unfavourable dominant, which it replaces. It is obvious from the curve that rare genes are more often recessives than dominants, and this is borne out by the sex-linked defects in man, which are all recessives, as so far known. The region where selection is weak is important. It is the place where new and untried recessive mutations accumulate; these mutations may be made to appear by inbreeding. The effect of inbreeding is, not to create, but to bring to light these rare recessives, and it is the usual experience, both of animal breeders and of mankind, that such recessives are usually harmful defects. The strict religious avoidance of incest which has characterised civilised man from at least the time of Hammurabi, and probably for much longer, is a very reasonable outcome of the fact that the rare recessives in mankind include such alarming defects as albinism and deaf-mutism.

Why should these rare recessives be generally harmful? It must depend on the nature of the mutations which occur, for these are chiefly untried mutations which have not yet been tested by selection. The apparently harmful effects of inbreeding indicate that mutations are for the most part, and to the greatest extent, harmful ; for if mutations were generally beneficial, by inbreeding, which uncovers and reveals the rare recessives, we should expect to make great and rapid progress. But the reverse is what is observed. The experience of animal breeders is in full accord with this view ; inbreeding is always regarded as dangerous, as liable to produce defectives, but as a useful means of fixing in the breed the character of some animal of known and valuable qualities.

We have now passed over in very brief outline the main results of the biometrical research in human heredity and the interpretation which the Mendelian theory of inheritance puts upon them. I should have done less than justice to the important and laborious investigations of which I have made use, if I left the impression that the biometrical investigations have been superseded by Mendelian research. It appears to me highly probable that all inheritance in sexual organisms will be found to conform to the Mendelian scheme, and that Mendelian inheritance offers a simple and complete explanation of the biometrical facts. The facts, however, could not have been ascertained by the Mendelian method of research, which is only applicable to sharply defined characters. The biometrical method affords a means of studying the quantitative characters. These are the characters of principle interest to the plant and animal breeder in increasing the utility of our domestic species, to the eugenist in attempting to preserve the higher types in mankind, and, I would suggest, to the evolutionist in studying the origin of the living forms on this planet. In particular it appears to me that the biometrical results interpreted in the light of Mendelism give us very definite guidance with respect to evolutionary problems which are still subject to dispute.

For evolution to have taken place at all, mutations are necessary; the new characters which a species acquires must be built up of heritable changes in the germ plasm. This has led many speculations to be put forward on the assumption that the direction of evolution is governed by the direction of mutation. On Darwin's theory of Natural Selection the direction of evolution is quite independent of the direction in which mutations predominate. Indeed, it is generally assumed by Darwinians that the majority of mutations are unfavourable to survival, but that the favourable minority are selected and the species progresses in the direction of better adaptation to its conditions. The two other suggestions put forward to explain evolutionary change both depend on the direction in which mutations take place. On the Larmarckian theory the excessive use of an organ tends to cause the appearance of mutations in the germ plasm, the effect of which mutations is to make the organ in question to develop to a greater size in the offspring. The assumpton is that the environmental conditions can govern the direction in which mutations take place, and that the evolution of the species is in turn governed by the predominant direction of mutations. On a third theory, known as Orthogenesis, the direction of evolution is also supposed to be governed by that of the mutations. It is not cleary stated on this theory to what the mutations are due, but it is supposed that they take place by small steps, and progressively ; type A mutates to a type B, type B to type C, and so on, the general trend of the steps A, B, C being an evolutionary sequence ; it is usually assumed in the direction of greater elaboration and complexity.

These theories have generally been criticised on the ground that mutations do not occur as they suppose ; but it appears to me that we know at present too little about mutations to settle the question on these lines. If we consider a mutation from A to B, it is not altogether obvious that back-mutations from B to A will necessarily be equally frequent, and if not, there is nothing to prevent us from saying that the organism has an orthonogenetic tendency to mutate in the direction AB. If we were to go further than this we should have to ask the supporter of orthogenesis to show that the state B tended to mutate to a state C, and that the mutation BC had in general similar bodily effects to the mutation AB. And of this further step no evidence whatever has been produced. Still, from what I have said, we have no reason for denying that the rudiments of what may be called an orthogenetic tendency exist in fact.

In the same way with Larmarckism ; we know very little about mutations and it would be rash to assume that use and disuse, or environmental conditions generally, do not somewhat affect their frequency. It is not impossible that in one environment the mutation from A to B may be more frequent than the mutation from B to A, while in a second environment the latter mutation may occur more frequently. We may admit that the rudiments of the Larmarckian assumption about mutations may occur in fact, though to be thoroughgoing Larmarckians we should have to admit further that the environment which caused, let us say, an increase in the muscles of blacksmiths' arms, also caused a tendency in his germ plasm to mutate in the special ways needed to increase the corresponding muscles of his children. And of this I consider the evidence negligible.

Still we need not rest our conclusion on such evidence ; we have still to ask, has the direction of mutation anything to do with the direction of evolution? In the past, when it was possible to assume that fresh mutations occurred in almost every individual of every generation, there was no reason to doubt, if mutation were to occur with great preponderance in one direction, that an evolutionary effect would be produced. But as soon as it is admitted that mutations are in fact very rare, and that the rate of mutation of any one gene is exceedingly small, then these theories become much less plausible.

In some cases the actual frequency of a particular mutation has been determined experimentally. Probably most genes mutate less than once in 100,000 individuals, but a few have been found more mutable, and in one special case, the Bar mutant in Drosophilia, the mutation from the defective Bar eye back to normal, takes place about once in 2,000 times. This is very much more frequent than any other case yet found.

If now we suppose that a mutation occurs with frequency one in 100,000, and that the opposite mutation occurs infinitely rarely, so that the bias in the direction of mutation is as great as possible ; suppose also that the mutation is opposed by the smallest possible selective influence, so that where the old form leaves 100 descendants, the mutant form will leave 99, a selective disadvantage of only 1%. What will be the effect on the species? It is easy to calculate that if the mutation is a dominant it will never appear in more than 1 in 500 of the species in general, and if it is a recessive, in about 1 in 2,000. There, as far as that mutation is concerned, evolution will cease. The mutation rates observed are so insignificant that even the slightest opposing selection brings their effect to nothing.

The organisms on which our knowledge of mutation rates is based, Drosophila and Maize, are extremely variable and very rich in mutations. There is certainly no reason to think that, in other species, much higher mutation rates will be found. Yet unless enormously higher mutation rates are available, any Larmarckian effect, or any Orthogenetic effect, would be entirely inoperative under conditions involving selection.

Against the theory of Orthogenesis there is also to be placed the entire lack of evidence of cumulative mutation ; indeed, one interesting fact about mutations points the other way. By far the commonest mutation in Drosophila, as I mentioned, is a mutation of the Bar factor which causes an abnormal eye, back to the normal condition. It was found that this mutation occurred only when a crossover had taken place at or near the Bar gene ; in the same circumstances a mutation in the opposite direction from Bar to Ultra-Bar is found to occur. It is probable that these two mutations in exactly opposite directions are consequences of the same event.

This is the only case of which so much is known ; if it is usual for mutations to occur simultaneously in opposite directions then it is manifest that the direction of evolution is not governed by the direction of mutation.

Very numerous and extensive efforts have been made to show that mutations may be produced by environmental effects. Some have been rejected as actually fraudulent, and there is, I believe, only one case in which it does appear to have been possible to induce a mutation with something like the frequency needed to contribute any evolutionary effect. In Guyer's experiments with rabbits, he seems to have produced a recessive mutation affecting the eyes in a fair proportion of the offspring of does subjected to a very artificial procedure. The experiment is of importance as showing that by sufficiently intimate interference with the developing embryo mutations may perhaps be induced with high frequency. The experiment does not, of course, demonstrate any evolutionary effect by analogous processes in nature, or that there is in general any correspondence between the effect of environment on the body, and its effect, if any, upon the germ plasm. I mention it here because it is the only known exception to the general rule of the rarity of mutations, and because, as I have tried to show, the consequences of that rule are of some importance in evolutionary theories.

SUMMARY.

Mendelism is the only type of inheritance yet demonstrated in fully investigated cases ; it is, however, theoretically possible that blending inheritance might exist in quantitative characters. The only quantitative characters which have been sufficently studied are those of Man, and here there is definite evidence both of segregation and of dominance. This suggests strongly that quantitative characters also are transmitted by Mendelian factors. If all inheritance falls within the Mendelian scheme, then mutations must be exceedingly rare events. Pure line experiments demonstrate that mutations are in fact very rare, and consequently that selection is the only agency by which species can be modified to any appreciable extent. This conclusion gives a special importance to the study of the nature of the selection actually in progress in civilised man.